CHAPTER 34
MOLECULAR & CELLULAR RADIOBIOLOGY

Radiation Interaction With Water
- The principal radiation interaction in the body

In Vitro
- Irradiation outside of the cell or body

In Vivo
- Irradiation with the cell or body

IRRADIATION OF MACROMOLECULES

Solution
- A liquid that contains dissolved substances

Three Major Effects When Macromolecules Are Irradiation in a Solution In Vitro
- Main-chain Scission, Cross-linking & Point Lesion

Main-Chain Scission
- The breakage of the backbone of the ling-chain macromolecules
- *Result:*
  - Reduction of a long, single molecule into many smaller molecules
- *Effects:*
  - Reduces the size of the macromolecules
  - Reduces the viscosity of the solution
    - Very thick & slow to flow
- *Measurement of Viscosity:* determines the degree of main-chain scission

Cross-Linking
- Process of side spurs created by irradiation & attached to a neighboring macromolecules or to another segment of the same molecule
- *Effect:* increases the viscosity of the macromolecular solution

Point Lesion
- Any change that results in the impairment or loss of function at the point of a single chemical bond
- Not detectable

At low radiation doses, point lesion are considered to be the cellular radiation damage that results in the late radiation effects observed at the whole-body level!

Catabolism
- The reduction of nutrient molecules for energy

Anabolism
- The production of large molecules for form and function

Metabolism consists of catabolism and anabolism!

Translation
- Process of forming a protein molecule from messenger RNA

Transcription
- Process of constructing mRNA

Proteins
- More abundant than nucleic acids
- Less radiosensitive than nucleic acids

DNA
- The most important molecule in the body
- Not abundant in the cell

DNA is the most radiosensitive molecule!

G_1 Portion of Interphase
- Deoxyribose, phosphate & base molecules accumulate in the nucleus
- DNA is in familiar double-helix form

S Portion of Interphase
- The DNA separates like a zipper
- Two daughter DNA molecules are formed

Chromosomes
- Control the growth & development of the cell

MOLECULAR & CELLULAR RADIOBIOLOGY

Radiation Effects on DNA

- Chromosome aberration or cytogenetic damage
- Abnormal metabolic activity
- Structural change

Type of Chromosome Aberrations

- Terminal deletion
- Dicentric formation
- Ring formation

Unobservable Radiation Response of DNA

- Main-chain scission with only one side rail severed
  - *Result:* structural change
- Main-chain scission with both side rail severed
  - *Result:* structural change
- Main-chain scission & subsequent cross-linking
  - *Result:* structural change
- Rung breakage causing separation of bases
  - *Result:* structural change
- Change in or loss of a base
  - A molecular lesion of DNA
  - Destroys the triplet code
  - May not be reversible

Point Lesion

- A molecular lesion of DNA
- Critical Consequence: the transfer of incorrect genetic code to one of the two daughter cells

Three Principal Observable Effects

- Cell death
- Malignant disease
  - Molecular level
  - Linear, nonthreshold dose-response relationship
- Genetic damage
  - Molecular level
  - Linear, nonthreshold dose-response relationship

Radiolysis of Water

- Dissociation of water into other molecular products as a result of irradiation
- Initial Result
  - *Ion Pair:* HOH^+ & e^-
- Final Result
  - *Ion Pair:* H^+ & OH^-
  - *Two Free Radicals:* H* & OH*

Irradiation of Water

- It represents the principal radiation interaction in the body

Free Radical

- An uncharged molecule that contains a single unpaired electron in the other shell
- *Lifetime:* < 1 ms

Hydrogen Peroxide

- Poisonous to the cell & therefore acts as a toxic agent
- *Chemical Formula:* H_2O_2
- *Formed By:*
  - $HO^* + HO^*$ or
  - $HO^*_2 + HO^*_2$

Hydroperoxyl Radical

- The principal damaging product after radiolysis of water along with Hydrogen peroxide
- *Chemical Formula:* HO^*_2
- *Formed By:* $H^* + O_2$

Organic Molecules

- *Symbol:* RH

Organical Free Radicals

- H^* & R^*
  - *Formed By:* RH + irradiation
- RO^*_2
  - *Formed By:* $R^* + O_2$

DIRECT & INDIRECT EFFECTS

Direct Effect

- If the initial ionizing event occurs on the target molecule

CHAPTER 34
MOLECULAR & CELLULAR RADIOBIOLOGY

Indirect Effect

- If the initial ionizing event occurs on a distant, noncritical molecule
- The energy is transferred to the target molecule

The principal effect of radiation on humans is indirect!

Target Theory

- For a cell to die after radiation exposure, its target molecule must be inactivated
- It was used to represent cell lethality
- It can be used to describe nonlethal radiation-induced cell abnormalities

DNA is the target molecule!

Target

- An area on the cell occupied by the target molecule or by a sensitive site on the target molecule

Hit

- Radiation interaction with the target or molecules
- It occurs through both direct & indirect effect
- It isn't simply an ionizing event, but rather an ionization that inactivates the target molecule

Direct & Indirect Effects

- *Low-LET Radiation & Absence of Oxygen:*
    - Low probability of hit on the target molecules
        - *Rationale:* relatively large distances between ionizing event
- *Low-LET Radiation & Presence of Oxygen:*
    - High probability of hit on the target molecules
        - *Rationale:*
            - Formation of free radical
            - Enlarged volume of effectiveness surrounding each ionization
- *High-LET Radiation & Absence of Oxygen:*
    - High probability of a hit by direct effect
        - *Rationale:* close distance between ionization event
- *High-LET Radiation & Presence of Oxygen:*
    - Does not result in additional hits
        - *Rationale:* the maximum number of hits has already been produced by direct effect with high-LET radiation

CELL SURVIVAL KINETICS

Cell Cloning

- Process by which normal cells produce a visible colony in a short time

The lethal effects of radiation are determined by observing cell survival, not cell death!

Two Models of Cell Survival

- Single-Target, Single-Hit Model
- Multi-Target, Single-Hit Model

Single-Target, Single-Hit Model

- It applies to biologic targets such as enzymes, viruses & bacteria
- *Equation:*
    - $S = N/N_o = e^{-D/D_{37}}$

Radiation interacts randomly with matter!

D_{37}

- When the radiation dose reaches a level sufficient to kill 63% of the cells (37% survival)
- A measure of the radiosensitivity of the cell
- *Low D_{37}:* highly radiosensitive
- *High D_{37}:* highly radioresistant

If there were no wasted hits (uniform interaction), D_{37} is the dose that would be sufficient to kill 100% of the cells!

CHAPTER 34
MOLECULAR & CELLULAR RADIOBIOLOGY

Multi-Target, Single-Hit Model

- It applies to more complicated biologic system such as human cells
- *Equation:*
  - $S = N/N_0 = 1 - (1 - e^{D/D_0})^n$
- It represents a threshold

Cell Survival

- *Very Low Radiation Dose:* nearly 100%
- *High Radiation Dose:* fewer cells survive
  - *Rationale:* more sustain a hit in both target molecules
  - *Survived Cells:* have one target hit
  - *Dose-Response Relationship:* appear as single-target, single-hit model

D_0

- The mean lethal dose
- A constant related to the radiosensitivity of the cell
- It is equal to D_{37} in the linear portion of the graph
- *Large D_0:* radioresistant cells
- *Small D_0:* radiosensitive cells

Extrapolation Number

- The target number

D_Q

- The threshold dose
- A measure of the width of the shoulder of the multitarget single-hit model
- It is related to the capacity of the cell to recover from sublethal damage
- *Large D_Q:* the cell can recover readily from sublethal radiation damage

Sublethal Damage

- A damage that must be accumulated before the cell dies
- *Wider Shoulder:*
  - More sublethal damage that can be sustain
  - The higher the value of D_Q

Split-Dose Irradiation

- Designed to describe the capacity of a cell to recover from sublethal damage

CELL CYCLE EFFECTS

Cell-Cycle Time/Cell Generation Time

- The average time from one mitosis to another
- *Human Cells:* approximately 24 hrs
- *Neurons:* hundreds of hrs
  - do not normally replicate
- Longer Generation Time
  - *Results From:* lengthening of the G_1 phase of the cell cycle

G_1 is the most time variable of cell phases!

Age-Response Function

- The pattern of change in radiosensitivity as a function of phase in the cell cycle
- *Mitosis:*
  - The most sensitive
  - Lower fraction of surviving cells
- *G_1-S Transition:* the next most sensitive
- *Late S-Phase:* the most resistant

Human cells are most radiosensitive in M & most resistant in late S!

LET, RBE & OER

Linear Energy Transfer (LET)

- *At Very High LET:* cell survival kinetics follows the single-target, single-hit model
  - *Examples:* alpha particles & neutrons
- *At Low LET:* cell survival kinetics follows the multi-target, single-hit model
  - *Example:* x-rays
- *Mean Lethal Dose:* greater after low-LET irradiation than after high-LET irradiation

Relative Biologic Effectiveness (RBE)

- *Formula:*

$$RBE = \frac{D_0 \text{ (x-radiation) to produce an effect}}{D_0 \text{ (test radiation) to produce the same effect}}$$

CHAPTER 34
MOLECULAR & CELLULAR RADIOBIOLOGY

Irradiation of mammalian cells with high-LET radiation follows the single-target, single-hit model!

Oxygen

- The most completely studied dose modifier
- *Presence of Oxygen:* maximizes the effect of low-LET radiation
- *Anoxic Cells:* requires higher dose to produce a given effect

Oxygen Enhancement Ratio

- Designed to measure the magnitude of the oxygen effect
- *Formula:*

$$OER = \frac{D_0 \text{ (anoxic) to produce an effect}}{D_0 \text{ (oxygenated) to produce the same effect}}$$

LET determines the magnitude of RBE & OER!